REMARKS

Claims 1. 3 – 8, 10 – 15, and 17 – 18 are currently pending. Claims 1, 8 and 15 are the pending independent claims. Claims 8 and 15 are amended herein and Claims 9 and 16 are cancelled. In the Office Action, Claims 1-18 were rejected as allegedly obvious from the combination of U.S. Patent 6,087,511 to Lin et al. ("Lin"), U.S. Patent 6,375,956 to Hermelin, et al. ("Hermelin") and U.S. Patent 6,004,477 to Nakegawa et al. ("Nakegawa"). These rejections were also made final.

Each of the foregoing rejections is respectfully traversed, and favorable reconsideration is requested in view of the above amendments and following remarks. As discussed in more detail below, nothing would have suggested to a person of ordinary skill that he/she should combine the disparate teachings of these three patents to provide amorphous atorvastation packaged under a substantially inert atmosphere and to enclose the pharmaceutical in a gas exchange substantially impermeable packaging material. Lin only uses a nitrogen blanket for dissolving crystalline atorvastin because the material is being solvated in tetrahydrofuran, a relatively dangerous solvent known to form explosive peroxides if exposed to air. Nothing is said in Lin about the use of any inert atmosphere or the like in subsequent steps of drying and packaging the material, etc. Lin's use of a nitrogen blanket over an oxygen-sensitive solvent used to dissolve crystalline atorvastatin plainly fails to teach that amorphous atorvastatin, after it has been manufactured, should be packaged in an inert atmosphere with a gas-impermeable package as claimed. Thus, for at least these reasons, Lin in combination with the other references plainly does not teach or suggest Applicants' invention should be withdrawn.

I. The Withdrawn Claims are Cancelled.

Applicants first note that they have cancelled Claims 19 and 20, which were previously restricted and withdrawn from consideration. The cancellation of these claims is with traverse to the propriety of the restriction, and without waiver of Applicant's right to further prosecute the subject matter of Claims 19 and 20 in a divisional application.

II. The Claims Patentably Distinguish Over the Cited References.

Again, all of the pending claims stand rejected as allegedly obvious over Lin as an alleged "primary" reference taken in combination with the teachings of Hermelin and

Nakegawa. It is respectfully submitted, however, that the purported combination of references is not "obviously" combinable relative to Applicants' invention and, in any event, the combined teachings fail to disclose or suggest the present invention as defined in Applicants' claims.

Turning to the independent claims, Claim 1 calls for a stable pharmaceutical composition which comprises a pharmaceutical formulation comprising amorphous atorvastatin calcium wherein the pharmaceutical formulation is packaged in a gas exchange non-permeable package wherein the packaging is carried out in an inert gas atmosphere. Claim 8 calls for a stable pharmaceutical formulation comprising amorphous atorvastatin calcium and pharmaceutically acceptable excipients which is stored in an inert atmosphere. Finally, Claim 15 calls for a stable amorphous active substance which is stored in an inert atmosphere, wherein the stable amorphous active substance is atorvastatin calcium.

The Examiner contends that Lin (the alleged "primary reference) discloses a process for making atorvastatin calcium (including amorphous atorvastatin) under nitrogen. He further contends that, in view of this disclosure, it would have been obvious to a person of ordinary skill to package the material under nitrogen such as in a gas-impermeable packaging material to prevent its reversion to distinct crystalline forms.

There are two main flaws with this argument. First, Lin only discloses dissolving *crystalline* atorvastatin calcium in a tetrahydrofuran solvent while under a nitrogen blanket. *Amorphous* atorvastatin calcium is not said to be formed until later when the atorvastatin calcium solution is *dried* under vacuum, not under a nitrogen blanket. Thus, Lin plainly fails to disclose or suggest the preparation of amorphous atorvastatin calcium under nitrogen, much less packaging of the material under an insert atmosphere.

Second, one of ordinary skill would not have viewed the use of a nitrogen blanket during the initial dissolution of the crystalline atorvastatin calcium in an oxygen-sensitive solvent as being related to the formation or maintenance of amorphous atorvastatin calcium. Instead, one of ordinary skill would have known that a nitrogen blanket was used to protect the tetrahydrofuran solvent from exposure to air. It is well known that tetrahydrofuran tends to form explosive peroxides when exposed to oxygen or air. *See, e.g.*, the attached MSDS for tetrahydrofuran and O.S.H.A. Guidelines for tetrahydrofuran. A person of ordinary skill would have known this, and would have simply assumed the nitrogen blanket was used by Lin to avoid exposure of the solvent to air. This suggests nothing about how any amorphous atorvastatin calcium should be packaged in a downstream operation. Lin does not even touch on how any end product should be packaged.

As for the supporting references, while Hermelin does deal with the packaging of pharmaceuticals in a blister pack, it says nothing whatsoever about the use of inert gases such as nitrogen within the packaging. Nor does Hermelin speak to the issue of how amorphous or any other form of atorvastatin should be packaged, and it certainly says nothing about how to package the material so as to maintain its amophism.

Finally, Nakagawa deals with oxygen and/or moisture scavengers. Nakagawa provides a list of a dozen or so products which may purportedly be protected using this oxygen absorption composition, including "pharmaceuticals." (Col. 10, line 49). But Nakagawa says nothing about the use of this composition to protect atorvastatin calcium for any purpose, much less protecting amorphous atovastatin against certain crystallizations upon exposure to air.

Moreover, Nakagawa's passing reference to the use of inert gases in packaging, taken in combination with the Lin and Hermelin patents, would not have lead one of ordinary skill to package atorvastatin calcium using an inert gas within a gas-impermeable package. As noted above, Lin simply teaches that amorphous atorvastatin calcium may be produced under vacuum conditions. Thus, if a person of ordinary skill was trying to devise a packaging or other storage system to protect the amorphous atorvastatin calcium made according to Lin, he or she would have been lead to follow Lin's indication to vacuum pack the amorphous atorvastatin calcium after the solvent had been removed, etc., rather than to package it under an insert gas atmosphere. There is no reason why a person of ordinary skill interested in packaging amorphous atorvastatin would have been led by Nakagawa to use inert gas packaging as claimed to avoid "morphing" of the desirable amorphic form of the atorvastatin material to certain crystalline forms while residing in the package. Nakagawa teaches nothing about the impact of any particular packaging technique on the maintenance of amorphous atorvastatin against crystallization.

In sum, the person of ordinary skill would have quickly recognized Lin's use of a nitrogen gas blanket over the tetrahydrofuran solvent used to dissolve crystalline atorvastatin as a conventional measure to avoid forming explosive peroxides. This uncontroversial reference in Lin to a well-known safety measure for use in the dissolving of atorvastatin crystals in a dangerous solvent and Lin's subsequent vacuum drying of what is said to be amorphous atorvastatin says nothing that would have led a person of ordinary skill to the realization that one should package the amorphous atorvastatin product in an inert atmosphere in a gas-impermeable package as claimed in the present application. The other references represent isolated teachings pertaining to other aspects of how to package various materials, but they would not have led a person of ordinary skill to modify the Lin process according to Applicants' claims.

In light of the foregoing, the present amendment is believed to place the application in a condition for allowance and entry of the foregoing amendments and allowance of the Claims 1, 3 – 8, 10 – 15, and 17 – 18 is respectfully solicited. Applicants therefore urge the Examiner to reconsider the application, to withdraw the rejections, and to issue a notice of allowance at the earliest possible convenience.

In the event this response is not timely filed, Applicants hereby petition for the appropriate extension of time and request that the fee for the extension along with any other fees which may be due with respect to this paper be charged to our Deposit Account No. 12-2355.

Respectfully submitted,
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